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HARMONIZING HORMONES

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THE mechanism of coordination within the animal body is one of the most subtle of all the organ systems of the higher animals, as it is one of the subtlest properties of the microscopic body of the protozoa. What it is in the single cell of the Paramecium, for example, that enables all the cilia covering its body to beat harmoniously in order to propel the organism either forward or backward is quite unknown. Our ignorance we cover by saying it is a property of the living substance to adapt itself to its environment and hence to advance or retreat according to the stimuli it receives. I have no desire at this time to inquire into this question of adaptation, interesting though it be, nor have I any desire to become involved in the discussion of a possible "vital principle" at work to keep the organism behaving as a perfectly unified body capable of maintaining itself in a changing environment.

The problem I would consider very briefly has to do with the visible or physical coordinators that can be demonstrated in the laboratory and that do not lead us at once into the realm of metaphysics.

There are three well defined coordinating systems in the higher animals. The simplest is made up of the connective tissues which hold the different parts of the body in proper spatial relations to each other, which exert pressures and tensions on different parts and prevent the mechanical interference of one part with another. Ligaments and bones by their special forms and attachments prevent us from wringing our own necks. In addition to the connective tissues, which are mechanical coordinators, the muscles may also be mentioned. The muscles of the neck must be strong enough to keep the head balanced and the tongue, though it may be "hung in the middle" in some of us must not be too large to fit comfortably within the mouth cavity. The second and far and away the most complex system of coordination is the nervous system which has evolved in the course of the history of living things to an elaborateness beyond that of any other. Coordination by means of the nervous system is brought about by the peculiarly specialized property of nerve cells of transmitting certain changes along their length so that the modification of one part of the body by a stimulus is transmitted to other distant parts and throws them into activity. The exact nature of these nerve impulses is still quite problematical but there has recently come to light evidence of their chemical nature since carbon dioxide is liberated more abundantly by a nerve along which impulses are passing than by one not active. The third form of coordinator in the body is the circulatory system by means of which materials are transported through the medium of the blood and lymph. By virtue of the rapid movement of the blood stream, all parts are furnished with a uniform nutriment and oxygen supply and washed free of accumulated wastes, and at the same time bathed with special chemical substances which modify the action of different parts of the body.

It is only very recently that the full significance of this last class of coordinators has been realized and it is to this system that I would call your attention specially. Within the past few years the energies of a great number of physiologists have been directed to certain specialized organs having the structure of glands but not communicating with any free surface by means of ducts. These organs secrete internally, directly into the blood stream from which they have derived the raw materials from which the hormone is secreted. The effects on neighboring organs of the products of other organs has been studied with great earnestness for some years, but our knowledge is still in its infancy. From the medical point of view there have been some remarkable advances made in this field. As Sir William Osler said recently, medicine has made no more brilliant advance than in the cure of certain diseases of these ductless glands.

One of the most important hormones which is produced by every living cell in the body is carbon dioxide. This is the normal product of cellular activity and affords a kind of measure of the vitality of a part. Resting, inactive cells produce comparatively little; actively contracting muscles or secreting glands produce large quantities. This waste matter, the product of the metabolism of the cells, is poured into the blood to be eliminated finally in the lungs. But before it is finally got rid of, it stimulates the respiratory center of the brain which activates the respiratory muscles. The more active the respiratory center, the more rapid and deep is the respiration. There is a most perfect coordination between the respiratory activity and the muscular activity of the body generally so that the quantity of carbon dioxide in the blood is maintained practically constant. Although breathing is under the control of the will within limits, we ordinarily respire involuntarily and unconsciously, and we take a breath only when the blood reaching the respiratory center of the brain contains an excess of carbon dioxide and stimulates it to greater activity; a fact which may be proved by any one most readily. Sitting quietly with watch in hand, the experimenter breathes rapidly and moderately deeply for from one half to one minute thus ventilating the lungs thoroughly. Then without trying to hold the breath he will note how long an interval passes before the slightest impulse to breathe is felt. In this case, by the thorough ventilation of the lungs more than the normal quantity of carbon dioxide passes out of the blood and is exhaled so that the blood reaching the respiratory center is abnormally poor in CO_2. The interval, until the impulse to breathe again is felt, represents the time it takes for carbon dioxide to accumulate in the blood to the normal amount. Conversely, the inhalation of carbon dioxide leads to more rapid and forced breathing because of the over-stimulation of the respiratory center. Before the young mammalian is born it does not breathe air through the lungs; in fact, its lungs do not begin to function until the infant is separated from the maternal blood circulation and the carbon dioxide produced by the activity of its cells has accumulated sufficiently in the blood to throw the respiratory center into activity and in consequence the muscles by means of which the air is changed in the lungs. This, of course, is simply a matter of seconds.

That it is the composition of the blood which determines the activity of the respiratory muscles may also be demonstrated in another way. The lungs of birds are so connected with air spaces which extend through the bones that it is possible to pass a continuous stream of fresh air through them by connecting the cut end of one of the larger bones with a suitable pump. Under the circumstances, the bird makes not the slightest respiratory movement for an indefinite time since its blood is maintained in a perfectly normal arterial condition, with an abundance of oxygen in it and unable to stimulate the respiratory center.

Another most clearly proved chemical harmonizer, which makes the pancreas secrete at the moment its secretion is needed, is the substance secretin which is formed in the intestine by the stimulation of the intestinal wall by an acid. This substance is carried to the pancreas in the circulation and causes that organ to secrete pancreatic juice, the most important digestive juice. The stimulation of the pancreas by some material transported thither rather than by nervous stimulus has been proven in several ways. All the nerves connected with an isolated loop of intestine are cut, so that no impulses can pass from the stimulated part of the intestine, but the blood vessels are left intact. An acid, like the acid of the gastric juice, is introduced into this isolated part of the intestine and the flow of pancreatic juice is noted. The increase of the flow of pancreatic juice is quite as great as when the nerves are not cut. Again, it has been found that the blood leaving the intestine which has been stimulated by an acid has the power of stimulating the flow of pancreatic juice in a second animal into whose blood vessels this blood is injected. It has been demonstrated also that acid in the blood alone has no such effect on the flow of pancreatic juice. Here we have a clear example of harmonious, purposeful action; namely, the secretion of pancreatic juice at the time that the contents of the stomach pass into the intestine, effected through a definite chemical substance manufactured in the intestine under the influence of an acid and transported to the pancreas.

Some very interesting cases of accurate coordination through chemical means have been noted in the development of the embryo from the egg. Let me illustrate with some experiments on the development of the eye of the tadpole. You may recall that the fine coordination displayed by the development of the eye was a stumbling block to Darwin in the way of the general acceptance of the theory of natural selection. The experimenter, however, has shown that to some extent this beautiful and complex coordination of parts is accomplished by chemical substances produced by certain organs. Before explaining the experiments, it will be necessary to describe very briefly the embryology of the eye. At a very early age before the body form of the embryo has been established and before many organs have been laid down, the brain broadens out in the form of a small conical projection on each side. The apex of this cone finally reaches the level of the skin. This swelling is known as the optic vesicle and from it is derived the portion of the eye which is sensitive to light, the retina. The bit of skin in contact with the apex of the optic vesicle sinks down beneath the surface like a little cup or pit, pushing the optic vesicle down with it, just as one might push in one side of a rubber ball with the thumb. The margins of this depression finally close together forming a hollow ball which becomes separated from the skin. This later becomes the lens of the eye. These are facts which could be demonstrated to you in a half hour in the laboratory. The lens of the eye, of course, is very different from the skin and if we did not know its embryological history we would hardly guess that it was derived from the skin. The embryologist used to think that the bit of skin which came to lie directly over the optic vesicle was unlike the rest of the skin, being endowed with special powers of forming the crystalline lens of the eye, and the mystery was, how it chanced that these lens-potentialities were accumulated at exactly the right spot and that there did not occur at times stray lenses scattered about on other parts of the body. The experimentalist, however, who has done so much to destroy illusions and push further back the limits of the mysterious, has shown that the formation of the lens depends entirely upon the contact of the optic vesicle and that any part of the skin under the influence of this structure will develop into a lens. Under the dissecting microscope with very fine needles it is possible to operate on the young tadpole before the eye is formed and to transplant the optic vesicle to some other part of the body. The results of this very drastic treatment are that any part of the skin which overlies the transplanted optic vesicle will form a lens. Any embryonic skin of the right age apparently has the power of developing into a lens under the proper stimulus. In fact the experimenter has gone so far as to graft two tadpoles of different species in such a way that the optic vesicle of one comes to lie directly beneath the skin of the abdomen of the other. But even here the skin of the abdomen of the strange tadpole developed a lens in a perfectly orthodox fashion.

Darwin today would not be so mystified over the question of how the different layers of tissue of different degrees of transparency and refraction chanced to occur in the right relations to each other to form a complex purposeful organ like the eye. The difficulty to-day is to explain how the skin of the embryo is endowed with such wonderful powers and how the optic vesicle is able to call forth such a complex response.

The phenomenon of internal secretion, that is, the discharge of substances manufactured by an organ directly into the blood passing through the organ and not to a free surface, was discovered by the great French physiologist, Claude Bernard, in 1876, when he demonstrated that the liver manufactures sugar and pours it constantly into the blood passing through that organ. Besides these organs which only incidentally to other functions secrete into the blood, like the liver, the pancreas, the sex glands and the developing fetus in the mammal, there are certain organs specialized for this purpose alone. These are called ductless glands, because they have no outlet to a surface, or endocrine organs, that is, organs secreting to the inside. The most important of these are the pituitary body, situated on the under side of the brain next to the roof of the pharynx and tucked into a little pocket on the floor of the skull; the pineal body, on the upper side of the brain but buried deep in the crease between the two halves of the cerebrum; the thyroid gland situated on the front of the throat just below the "Adam's apple" and enlarged in goitre; the thymus gland situated in front of the heart, from which the true "neck sweetbreads" are taken; and the adrenal bodies situated just above the kidneys.

The ductless glands just enumerated seem to have the most marked effect upon growth, development, and nutrition. Some of them, especially the adrenal body, also have a marked effect upon the blood pressure.

The thyroid gland influences powerfully the growth of the body and the rate at which the mature state is reached.

A few years ago one of our American experimenters showed that the growth of the tadpole may be stopped almost immediately by feeding thyroid gland. At the same time that the increase in size ceases, the transformation of the tadpole into a frog goes on with increased speed. Tadpoles were obtained which had the fore legs in fifteen days from the time that they issued from the egg while ordinarily they appear only after about four months. The action of the thyroid gland on the human subject seems to be somewhat different from that just described although its action affects development. The distressing disease, cretinism, characterized by the squat stature and low mentality, with puffy skin and bleary eyes, is the result of insufficient activity of the thyroid which may be made good by feeding thyroid glands from oxen or sheep. Thyroid feeding is sometimes employed to reduce obesity, as under its stimulus more rapid oxidation of the tissues takes place. Thyroid fed to immature rats retards growth. Rats fed thyroid gland do not gain weight as rapidly as normal ones. To one-half of a litter kept under conditions as nearly like the other half as possible were fed small quantities of thyroid. In three or four days the thyroid individuals gained only 4.2 gms. on the average as compared with 10.1 gms. for those not specially fed.

Another organ which has a very marked effect upon growth is the pituitary body, a small structure which is attached to the under side of the brain and which originates in the embryo from the roof of the mouth. When this gland secretes more than the normal amount in childhood before growth is completed, gigantism results and the child continues its growth beyond the normal and becomes a giant. The overactivity of the same gland later in life when normal growth is complete leads to a disease known as acromegaly in which the extremities of the body alone grow abnormally. Conversely, if the pituitary body is removed or if it is not sufficiently active on account of disease, there follows a condition known as infantilism, characterized by the development of much fat beneath the skin and more or less atrophy of the sexual organs.

Regarding the function of the thymus we are especially in the dark. As is well known it degenerates before the adult condition is attained and it may be removed from young animals apparently without causing any modification in the rate of growth or any special symptoms of any kind. The feeding of thymus gland to tadpoles has been found, however, to have a marked effect upon growth, prolonging the period of growth and inhibiting the metamorphosis of the tadpole.

The action of the adrenal bodies has already been alluded to. The removal of the organs is followed by death in about 36 hours in the mammals ordinarily used for experimental purposes like dogs, cats, rabbits, and the like. When the adrenals are diseased, a number of definite symptoms known as Addison's disease appear; the skin assumes a coppery color, there is great muscular weakness and lowering of the temperature of the body. The application of the extract of the gland—adrenalin—to a bleeding or inflamed part is followed at once by a constriction of the capillary blood vessels and a blanching of the part. This property, of course, makes the extract of great value to the surgeon in operations in which there is profuse bleeding from many tiny blood vessels, like many operations on the nose. So powerful is the hormone of the adrenal body that one part of adrenalin in one hundred million of Ringer's solution produces marked effect on the contraction of involuntary muscle.

The pineal body, which Descartes thought was the seat of the soul of man, has a most obscure function which cannot at present be clearly defined. The removal of the organ is very difficult without serious injury in the operation. When it is successfully removed without injury to the animal there has been found to be in some cases a precocious development of the sexual organs but in other experiments the effects have been negative.

The ductless glands seem to be more or less closely related to each other in function so that the removal of one may be accompanied by changes in others, but it is apparent that there is much still to be learned regarding the exact working of these very subtle organs. The fact, however, that the precise functions of some of these organs have not been exactly determined does not mean that they have little effect upon the organism as a whole. What has just been said regarding the pituitary, suprarenals, and thyroids shows that the contrary is the fact.

Considering the organs which only incidentally secrete internally, the pancreas exhibits a very interesting harmonizing action. The function of the pancreas is not only the secretion of a digestive juice which performs the great bulk of the digestion of food in the intestine, but also the secretion into the blood of something which enables the sugar absorbed from the intestine to be stored in the liver until needed in the active organs of the body. If the pancreas is removed entirely, diabetes appears at once due to the failure of the liver to remove the sugar from the blood. In order to determine that this condition is not due simply to the elimination of the pancreatic juice from the alimentary canal, the experiment has been made of simply tying off tightly the duct leading from the pancreas to the intestine, but not interfering with the circulation of the blood through the organ, and also of grafting the pancreas which has been cut out, on some other part of the body so that blood will pass through it. In both these experiments diabetes does not appear and we must conclude that the pancreas secretes into the blood a substance which enables the liver to store up grape sugar.

The effects of the reproductive organs upon the body as a whole have been known in a general way from time immemorial. Especially in the male sex have the reproductive organs been removed for economic or social reasons. Emasculation in the human subject when performed in early youth prevents those changes from taking place which normally occur at puberty, such as growth of hair on various parts of the body, the growth of the larynx with the consequent lowering of the pitch of the voice, and the growth of the chest. It has been said also that in oxen and horses the removal of the male sexual organs at an early age causes the haunch bones to change to the female type. It has been known for years that if the very young male deer is castrated, the antlers never appear and if the operation is performed when the antlers have already begun to develop, they fail to reach their normal size and remain covered with the velvet, like young antlers. In the adult deer castration causes the antlers to be shed precociously and they are replaced, if at all, by imperfect antlers which are never renewed. Thus we see that the complex changes involved in the development of the antlers are dependent upon the presence of something supplied by the sex glands of the male.

The female sex organs are no less potent in determining the course of development. One experimenter removed the testes of a guinea pig and a rat and replaced them with ovaries from a female. The presence of the ovaries in the body of the emasculated male led to a remarkable development of the mammary glands and a change in the proportions of the skeleton to more nearly those of the female. Another important change is that the size of the feminized males is less than that of the normal castrated males, showing that there is something produced by the ovary which prevents the normal growth of the male. These experiments are not numerous but they indicate something of the power of the sexual organs to determine by their internal secretions the growth and relative size of parts of the body.

Equally marked effects have been noted in the case of birds. The desirable effects of removing the male organs have been known for many years and capons have been highly esteemed as delicacies. It is well known, of course, that the removal of the male organs in poultry leads to increased size and deposition of fat. Notwithstanding, the male plumage with all the secondary sexual characters appear as in normal birds. During the past few years the experiment of removing completely the ovaries from a female bird has been successful. In this case the ovaries were removed from a very young Mallard duck, in which the plumage of the male and female are very different. It was found that the plumage of the spayed female became similar to that of the male.

The developing fetus within the uterus of the female exercises an important effect upon the development of the milk glands so that the latter are able to supply an abundant nourishment for the young which are to be born shortly. This effect is produced by the discharge of some substance into the blood stream of the mother through the placenta. This has been demonstrated with rabbits by injecting into the blood vessels of a virgin rabbit, in which the milk glands are practically invisible, the extract of a fetus taken from a pregnant female.

The injection is followed by a rapid growth of the glands. That this effect is produced directly upon the milk glands and not indirectly through the action of the uterus and ovaries has been shown by making the injection after the removal of those organs. The effect upon the milk glands is just as marked as when ovaries and uterus are present. A further confirmation of the harmonizing of the activity of the mammary glands and the needs of the body through hormones is afforded by the famous case of the Blazek sisters who were joined like the Siamese twins with blood vessels united but with entirely separate nervous systems. In spite of the absence of nervous connections between the two, pregnancy in the one produced a normal growth of the mammary glands of the other, and with the birth of the child the secretion of milk by the glands of the two sisters occurred. A third method of demonstrating the chemical control of the mammary glands is by severing the spinal cord at the level from which the nerves going to the glands are given off, so that the nervous connections between the two ends of the mammary glands in such an animal as the dog whose glands extend along the entire length of the abdomen, are severed. In spite of this separation, however, secretion occurs simultaneously in all the glands.

Our knowledge of the presence and action of hormones in the blood is in its infancy. There can be little doubt that further investigations will prove that many more are working in the body than we dream of now and that their effects may be found to be of far more importance. The endocrine organs can not be supposed to allow of the complex development which the nervous system has experienced in the animal kingdom nor can it ever have the same far-reaching effects, but enough perhaps has been presented to show how the integration of the body as a whole is brought about by non-living products of cells circulating in the blood. In conclusion, however, we can hardly say that the physiologist, studying the chemical harmonizers of the body, has solved the problem of individuality, or that the conception of the animal body has been rendered more simple as a result of these discoveries. The explanation of the timely appearance of these harmonizers and the mechanism of the complex reactions to them is quite as difficult and perplexing as that of the harmonies themselves. The knowledge of these chemical bodies is an aid to us in pushing back further in the life cycle those forces or mechanical devices which are capable of producing the integrated living body, and the harmonizers of the body afford a mechanical explanation of many phenomena which in the past required a mystical or vitalistic explanation. The chemical harmonizers in their action and the response of the body to them are quite as baffling as the fact of harmonious action itself, so that pushing back the mystery only deepens it.